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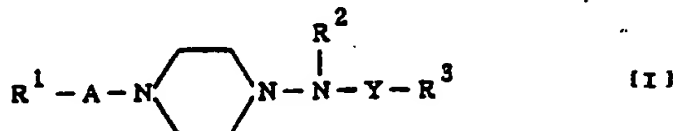
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(54) **NEW AMINOPIPERAZINE DERIVATIVES.**

(57) Compounds effective in enhancing the cholinergic activity, represented by general formula (I), and pharmaceutically acceptable salts thereof, methods for the preparation thereof, and pharmaceutical composition containing the same, wherein R¹ represents an optionally halogenated lower alkyl, aryl (lower) alkoxy, or heterocyclic group; R² represents a hydrogen atom or a lower alkyl group; R³ represents an optionally halogenated cyclo (lower) alkyl, aryl or arly (lower) alkyl group; A represents -CO-, -SO₂- or a lower alkylene group; and Y represents -CO-, -SO₂- -CONH-.



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TECHNICAL FIELD

This invention relates to new aminopiperazine derivatives and pharmaceutically acceptable salts thereof which are useful as a medicament.

BACKGROUND ART

Some piperazine derivatives have been known as useful anti-amnesia agents, for example, in G.B. Patent Application Publication No. 2 162 843 and EP Patent Application Publication No. 299 493, but the N-substituents of piperazine ring in these compounds do not contain amino group while our compounds are N-aminopiperazine derivatives.

DISCLOSURE OF INVENTION

This invention relates to new aminopiperazine derivatives and pharmaceutically acceptable salts thereof.

More particularly, it relates to new aminopiperazine derivatives and pharmaceutically acceptable salts thereof which have the potentiation of the cholinergic activity, to processes for the preparation thereof, to a pharmaceutical composition comprising the same, and to a method for the treatment of disorders in the central nervous system for human beings, and more particularly to method for the treatment of amnesia, dementia, senile dementia and the like.

One object of this invention is to provide new and useful aminopiperazine derivatives and pharmaceutically acceptable salts thereof which possess the potentiation of the cholinergic activity.

Another object of this invention is to provide processes for preparation of said aminopiperazine derivatives and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said aminopiperazine derivatives and pharmaceutically acceptable salt thereof.

Still further object of this invention is to provide a therapeutic method for the treatment of disorders in the central nervous system for human beings, and more particularly of amnesia, dementia, senile dementia and the like, using said aminopiperazine derivatives and pharmaceutically acceptable salts thereof.

The aminopiperazine derivatives of this invention are new and can be represented by the following general formula [I] :



wherein R¹ is lower alkyl, aryl, ar(lower)alkoxy or a heterocyclic group, each of which may be substituted with halogen,

R² is hydrogen or lower alkyl,

R³ is cyclo(lower)alkyl, aryl or ar(lower)alkyl, each of which may be substituted with halogen,

A is



-SO₂- or lower alkylene, and

Y is



-SO₂- or

and pharmaceutically acceptable salts thereof.

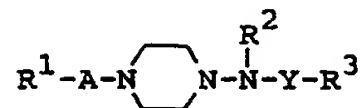
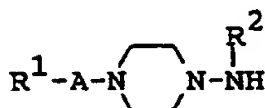
The object compound [I] or its salt can be prepared by processes as illustrated in the following reaction schemes.

Process 1

15

HO-Y-R³ [III]
or its reactive
derivative

20



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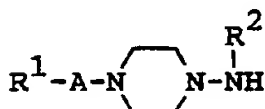
[II]
or its salt

[I]
or its salt

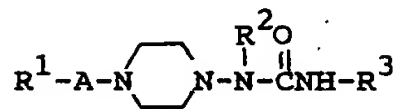
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Process 2

35



R³-NCO [IV]



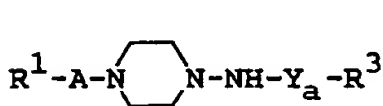
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[II]
or its salt

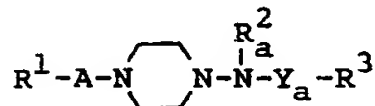
[Ia]
or its salt

Process 3

45



$\text{R}_a^2 - \text{X}$ [V]



50

[Ib]
or its salt

[Ic]

55 wherein R¹, R², R³, A and Y are each as defined above,
R_a² is lower alkyl,
Y_a is



5

or -SO₂-, and

X is an acid residue.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

70 The term "lower" is intended to mean a group having 1 to 6 carbon atom(S), unless otherwise provided.

Suitable "lower alkyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, or the like, in which preferable one is methyl.

Suitable "aryl" may be phenyl, naphthyl, tolyl, xylyl, mesityl, cumenyl, and the like, in which preferable one is phenyl or naphthyl.

15 Suitable "ar(lower)alkoxy" may be benzyloxy, phenethyloxy, phenylpropoxy, benzhydryloxy, trityloxy and the like.

Suitable "heterocyclic group" may include saturated or unsaturated, monocyclic or polycyclic one containing at least one hetero atom such as nitrogen atom, oxygen atom or sulfur atom.

20 The preferred examples of thus defined "heterocyclic group" may be unsaturated, 3 to 8-membered, more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4-nitrogen atom(S), for example, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridyl N-oxide, dihydropyridyl, tetrahydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, tetrazinyl, tetrazolyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

25 unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl, etc.;

saturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholino, sydnonyl, etc.;

30 unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, etc.;

35 unsaturated, condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

40 unsaturated, condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothieryl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s), for example benzofuranyl, etc.; or the like.

Suitable "cyclo(lower)alkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

Suitable "ar(lower)alkyl" may be benzyl, phenethyl, phenylpropyl, benzhydryl, trityl, and the like.

45 Suitable "lower alkylene" may be methylene, ethylene, propylene, pentamethylene, hexamethylene, and the like.

Suitable "acid residue" may include halogen (e.g. fluorine, chlorine, bromine, iodine), arenesulfonyloxy (e.g., benzenesulfonyloxy, tosyloxy, etc.), lower alkanesulfonyloxy (e.g. mesyloxy, ethanesulfonyloxy, etc.) and the like.

50 The above-mentioned "lower alkyl", "aryl", "ar(lower)alkoxy", "heterocyclic group", "cyclo(lower)alkyl" and "ar(lower)alkyl" may be substituted with halogen [e.g. fluorine, chlorine, bromine and iodine].

Suitable pharmaceutically acceptable salts of the object compound [I] are conventional non-toxic salts and include acid addition salt such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, 65 tartarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], a salt with an amino acid [e.g. aspartic acid salt, glutamic acid salt, etc.] and the like.

The processes for preparing the object compound [I] are explained in detail in the following.

Process 1

The compound [I] or its salt can be prepared by reacting a compound [II] or its salt with a compound [III] or its reactive derivative at the carboxy or sulfo group.

5 Suitable salts of the compound [II] may be the same as those exemplified for the compound [I].

Suitable reactive derivative at the carboxy or sulfo group of the compound [III] may include an ester, an acid halide, an acid anhydride and the like. The suitable examples of the reactive derivatives may be an acid halide [e.g. acid chloride, acid bromide, etc.]; a symmetrical acid anhydride; a mixed acid anhydride with an acid such as aliphatic carboxylic acid [e.g. acetic acid, pivalic acid, etc.]; substituted phosphoric acid [e.g. dialkylphosphoric acid, diphenylphosphoric acid, etc.]; an ester such as substituted or unsubstituted lower alkyl ester [e.g. methyl ester, ethyl ester, propyl ester, hexyl ester, trichloromethyl ester, etc.], substituted or unsubstituted ar(lower)alkyl ester [e.g. benzyl ester, benzhydryl ester, p-chlorobenzyl ester, etc.], substituted or unsubstituted aryl ester [e.g. phenyl ester, tolyl ester, 4-nitrophenyl ester, 2,4-dinitrophenyl ester, pentachlorophenyl ester, naphthyl ester, etc.], or an ester with N,N-dimethylhydroxylamine, N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxy-6-chloro-1H-benzotriazole, or the like. 15 These reactive derivatives can be optionally selected according to the kind of the compound [III] to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, 20 pyridine or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvent may be used in a mixture with water.

When the compound [III] is used in a free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, 25 thionyl chloride, oxalyl chloride, lower alkoxycarbonyl halide [e.g. ethyl chloroformate, isobutyl chloroformate, etc.], 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, or the like.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Process 2

30 The compound [Ia] or its salt can be prepared by reacting a compound [II] or its salt with a compound [IV].

Suitable salts of the compound [II] may be the same as those exemplified for the compound [I].

This reaction is usually carried out in a solvent such as dioxane, tetrahydrofuran, benzene, chloroform, 35 methylene chloride or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 3

40 The compound [Ic] can be prepared by reacting a compound [Ib] or its salt with a compound [V].

Suitable salts of the compound [Ib] may be the same as those exemplified for the compound [I].

The present reaction is preferably carried out in the presence of base such as an alkali metal (e.g. lithium, sodium, potassium, etc.), alkaline earth metal (e.g. calcium, etc.), alkali metal hydride (e.g. sodium 45 hydride, etc.), alkaline earth metal hydride (e.g. calcium hydride, etc.) and the like.

This reaction is usually carried out in a solvent such as N,N-dimethylformamide, diethyl ether, tetrahydrofuran, dioxane, benzene, toluene or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating, 50 The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

The object compounds [I] and pharmaceutically acceptable salts thereof possess strong potentiation of the cholinergic activity, and are useful for the treatment of disorders in the central nervous system for human beings, and more particularly of amnesia, dementia, senile dementia and the like.

55 In order to illustrate the usefulness of the object compound [I], the pharmacological test data of the compound [I] are shown in the following.

Anti-scopolamine-induced amnesia activity

Test Method :

Male Wistar rats (body weight 250-300 g, 23-31 per group) were used. The effect of the test compound on deficit of memory induced by scopolamine (a muscarinic acetylcholine receptor antagonist) in passive avoidance task was examined. The apparatus consists of an illuminated compartment attached to a dark compartment equipped with a grid floor. These compartments are separated with a guillotine door. The rat was placed in the illuminated compartment and 10 seconds after placing the rat, the guillotine door was raised. After the rat entered into the dark compartment, the rat was returned to its home cage (Habituation). 30 minutes after habituation, scopolamine hydrobromide (1 mg/kg) (Sigma Co. St Louis, MO, U.S.A.) was intraperitoneally (i.p.) administered. 60 minutes after habituation, the acquisition trial was carried out. The rat was again placed in the illuminated chamber. When the rat entered in the dark chamber, the guillotine door was closed and a 4mA scrambled electrical footshock was delivered for 3 seconds through the grid floor. Test compounds were intraperitoneally administered immediately after this training.

In the test trial given 24 hours after the training, the rat was placed again in the illuminated compartment and the response latency to enter into the dark compartment was measured to an extent of 300 seconds at the longest. Results were recorded as the mean latency of step through for each experimental group of rats. The effect of the test compound was presented as a percentage of the recovery. The calculation was based on the following equation.

$$\text{Percentage of Recovery (\%)} = \frac{A - B}{300 - B} \times 100$$

A : mean latency of test compound (sec)
B : mean latency of vehicle (sec)

Test Compounds :

- (a) N-(4-Acetyl-1-piperaziny)-4-fluorobenzamide
(b) N-(4-Benzoyl-1-piperaziny)-4-fluorobenzamide
(c) N-(4-Acetyl-1-piperaziny)-4-fluorobenzenesulfonamide

Test Results :

Percentage of Recovery (%)

Test Compound Dose (mg/kg)	(a)	(b)	(c)
0	0	0	0
0.1	23.0	26.4	20.4
0.32	24.6	29.5	26.8
1.0	40.3	19.7	34.5
3.2	39.2	41.5	50.2

For therapeutic purpose, the compound [I] and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solution, suspension, emulsion, or the like. If desired,

there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound [I] will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound [I] may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

10

To a mixture of 1-nitrosopiperazine (1.21 g) and pyridine (2.4 ml) in dioxane (18 ml) was added dropwise 2-thenoyl chloride (1.2 ml) in an ice bath. The mixture was stirred for one hour in an ice bath and then overnight at ambient temperature. The mixture was poured into a mixture of ethyl acetate (100 ml) and water (100 ml). The separated aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried and concentrated in vacuo. The residue was pulverized with diisopropyl ether to yield 1-nitroso-4-(2-thenoyl)-piperazine (1.78 g).

To a solution of 1-nitroso-4-(2-thenoyl)piperazine (1.78 g) in a mixture of acetic acid (8 ml) and water (8 ml) was added Zn powder (1.55 g) in several portions at 6-15 °C. The suspension was stirred for 1.5 hours below 10 °C. To the mixture was added acetic acid (4 ml) and Zn powder (780 mg) at 8-12 °C. The mixture was stirred for 2 hours at ambient temperature. To the suspension was added 17% aqueous sodium hydroxide solution (70 ml). The insoluble materials were filtered off. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution by 5% methanol in dichloromethane) to yield 1-amino-4-(2-thenoyl)piperazine (1.17 g) as a pale yellow syrup.

¹H NMR (CDCl₃, δ) : 7.48 (1H, dd, J = 1 and 5Hz), 7.31 (1H, dd, J = 1 and 4Hz), 7.07 (1H, dd, J = 4 and 5Hz), 3.83 (4H, t, J = 5Hz), 2.88 (2H, br.s), 2.70 (4H, t, J = 5Hz)

The following compound (Preparation 2) was obtained according to a similar manner to that of Preparation 1.

Preparation 2

1-Amino-4-(2-naphthoyl)piperazine
pale yellow syrup

¹H NMR (CDCl₃, δ) : 7.98-7.83 (4H, m), 7.65-7.45 (3H, m), 3.88 (2H, br.s), 3.62 (2H, br.s), 3.04 (2H, br.s), 2.68 (4H, br.s)

35

Preparation 3

To a solution of 1-[2-bis(4-fluorophenyl)-methoxy]ethyl]piperazine (1 g) in 1N-hydrochloric acid (3 ml) was added 1N-hydrochloric acid in order to adjust pH to 4. The mixture was stirred at 70-75 °C and therein a solution of sodium nitrite (0.31 g) in water (0.5 ml) was added dropwise. The mixture was stirred at 70-75 °C for one hour, cooled, and diluted with a mixture of diethyl ether and aqueous sodium bicarbonate solution. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluted with chloroform to yield 1-[2-bis(4-fluorophenyl)-methoxy]ethyl]-4-nitrosopiperazine (0.9 g) as an oil.

¹H NMR (CDCl₃, δ) : 7.28 (4H, dd, J = 5 and 9Hz), 7.02 (4H, t, J = 9Hz), 5.36 (1H, s), 4.28 (2H, t, J = 6Hz), 3.93-3.77 (2H, m), 3.62 (2H, t, J = 6Hz), 2.84-2.67 (4H, m), 2.58-2.43 (2H, m)

50

Preparation 4

To a solution of 1-[2-bis(4-fluorophenyl)-methoxy]ethyl]-4-nitrosopiperazine (0.9 g) in a mixture of acetic acid (2.4 ml) and water (1.2 ml) was added Zn powder (0.75 g) in several portions below 10 °C. After stirring for an hour below 10 °C, the mixture was further stirred for four hours at ambient temperature. The insoluble materials were removed by filtration and the filtrate was saturated with hydrogen sulfide. The precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was dissolved with chloroform, washed with saturated aqueous solution of sodium hydrogen carbonate and dried over sodium sulfate. After

evaporation of the solvent, 1-amino-4-[2-[bis(4-fluorophenyl)methoxy]ethyl]piperazine as an oil.

^1H NMR (CDCl_3 , δ) : 7.28 (4H, dd, $J=5$ and 9Hz),

7.00 (4H, t, $J=9\text{Hz}$), 5.32 (1H, s),

3.53 (2H, t, $J=6\text{Hz}$), 2.90-2.30 (12H, m)

5

Example 1

To a mixture of 1-acetyl-4-aminopiperazine dihydrochloride (540 mg) and 4-fluorobenzenesulfonyl chloride (535 mg) in dichloromethane (5 ml) was added triethylamine (1.2 ml) in a few minutes with stirring in an ice bath. After stirring for half an hour at the same temperature, the mixture was washed with brine, dried, and concentrated in vacuo. The residue was crystallized from ethanol and recrystallized from a mixture of ethanol and diethyl ether to yield N-(4-acetyl-1-piperazinyl)-4-fluorobenzenesulfonamide (360 mg) as white crystals.

mp : 185-186 °C

IR (CHCl_3) : 3400, 3300, 3005, 1642, 1638, 1596, 1498, 1460, 1256, 1240, 1170, 1155, 1094 cm^{-1}

Example 2

To a solution of 1-amino-4-benzoylpiperazine (1.1 g) and triethylamine (0.6 g) in dichloromethane (20 ml) was added dropwise 4-fluorobenzoyl chloride (0.86 g) with stirring in an ice bath. After stirring for one hour at the same temperature, the mixture was washed with 1N hydrochloric acid, dried, and concentrated in vacuo. The residue was crystallized from diisopropyl ether and purified by recrystallization from ethanol to give N-(4-benzoyl-1-piperazinyl)-4-fluorobenzamide (0.97 g) as white crystals.

mp : 206-207 °C

^1H NMR (CDCl_3 , δ) : 7.78 (2H, dd, $J=5$ and 9Hz), 7.43 (5H, s), 7.34 (1H, br.s), 7.12 (2H, t, $J=9\text{Hz}$), 3.96 (2H, br.s), 3.67 (2H, br.s), 3.03 (4H, br.s)

The following compound (Example 3) was obtained according to a similar manner to that of Example 1.

Example 3

30

N-(4-Benzenesulfonyl-1-piperazinyl)-4-fluorobenzenesulfonamide

mp : 190-191 °C

^1H NMR (CDCl_3 - CD_3OD = 1:1, δ) : 7.88 (2H, dd, $J=5$ and 9Hz), 7.78-7.57 (5H, m), 7.20 (2H, t, $J=9\text{Hz}$), 3.03-2.92 (4H, m), 2.75-2.66 (4H, m)

The following compounds (Examples 4-1) to 4-11)) were obtained according to a similar manner to that of Example 2.

Example 4

40

1) N-(4-Acetyl-1-piperazinyl)-2-fluorobenzamide

mp : 171-172 °C

IR (CHCl_3) : 3480, 3400, 3015, 1678, 1644, 1619, 1488, 1458, 1444, 1300, 1285, 1262 cm^{-1}

2) N-(4-Acetyl-1-piperazinyl)-3-fluorobenzamide

mp : 196-197 °C

45

IR (CHCl_3) : 3350, 3005, 1680, 1640, 1592, 1440, 1282, 1258 cm^{-1}

3) N-(4-Acetyl-1-piperazinyl)-4-fluorobenzamide

mp : 211-212 °C

^1H NMR ($\text{DMSO}-d_6$, δ) : 9.58 (1H, s), 7.84 (2H, dd, $J=6$ and 9Hz), 7.31 (2H, t, $J=9\text{Hz}$), 3.52 (4H, t, $J=6\text{Hz}$), 2.88 (2H, t, $J=6\text{Hz}$), 2.82 (2H, t, $J=6\text{Hz}$), 2.03 (3H, s)

50

4) N-(4-Acetyl-1-piperazinyl)cyclohexanecarboxamide

mp : 220-221 °C

IR (CHCl_3) : 3430, 3340, 2998, 2940, 2852, 1638, 1448, 1280, 1256, 1140, 1118, 998 cm^{-1}

5) N-(4-Acetyl-1-piperazinyl)-4-fluorophenylacetamide

mp : 163-164 °C

55

IR (CHCl_3) : 3440, 3340, 3300, 1670, 1640, 1510, 1440, 1282, 1258, 1158, 1140, 1120, 1000 cm^{-1}

6) N-(4-Phenylsulfonyl-1-piperazinyl)-4-fluorobenzamide

mp : 274-276 °C

^1H NMR (CDCl_3 - CD_3OD = 1:1, δ) : 7.86-7.58 (7H, m),

7.14 (2H, t, J=9Hz), 3.28-3.18 (4H, m),

3.07-2.98 (4H, m)

7) N-(4-Methylsulfonyl-1-piperazinyl)-4-fluorobenzamide

mp : 257-258 °C

5 ¹H NMR (CDCl₃-CD₃OD = 1:1, δ) : 7.80 (2H, dd, J=5 and 9Hz), 7.12 (2H, t, J=9Hz), 3.40 (4H, t, J=5Hz), 2.99 (4H, t, J=5Hz), 2.88 (3H, s)

8) N-[4-(2-Thienoyl)-1-piperazinyl]-4-fluorobenzamide

mp : 189-190 °C

IR (CHCl₃) : 3440, 3340, 3280, 3000, 1674, 1604, 1501, 1438, 1284, 1259 cm⁻¹

10 9) N-[4-(2-Naphthoyl)-1-piperazinyl]-4-fluorobenzamide

mp : 227-228 °C

IR (CHCl₃) : 3430, 3335, 2990, 1668, 1617, 1601, 1496, 1477, 1438, 1284, 1260 cm⁻¹

10) N-(4-Benzyl-1-piperazinyl)-4-fluorobenzamide

mp : 165-168 °C

15 ¹H NMR (CDCl₃, δ) : 7.77 (2H, dd, J=5 and 9Hz),

7.45-7.23 (5H, m), 7.10 (2H, t, J=9Hz),

3.41 (2H, s), 3.00 (4H, br.s), 2.72 (4H, br.s)

11) N-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-piperazinyl]-4-fluorobenzamide

mp : 141-144 °C

20 ¹H NMR (CDCl₃, δ) : 7.88-7.70 (2H, m), 7.28 (4H, dd, J=5 and 9Hz), 7.20-6.95 (6H, m), 6.90 (1H, s), 5.35 (1H, s), 3.60 (2H, t, J=6Hz), 3.10-2.60 (10H, m)

Example 5

25 To a solution of 1-acetyl-4-aminopiperazine dihydrochloride (540 mg) in dichloromethane (5 ml) was added dropwise triethylamine (0.8 ml) followed by addition of 4-fluorophenylisocyanate (377 mg) in dichloromethane (2.5 ml) with stirring in an ice bath. After stirring for 100 minutes at the same temperature, a mixture of dichloromethane (15 ml) and methanol (3 ml) was added to the reaction mixture. The mixture was washed with brine, dried, and concentrated in vacuo. The residue was crystallized from

30 ethanol to yield N-(4-acetyl-1-piperazinyl)-N'-(4-fluorophenyl)urea (500 mg).

mp : 210-211 °C

¹H NMR (CDCl₃, δ) : 7.98 (1H, s), 7.40 (2H, dd, J=5 and 9Hz), 7.00 (2H, t, J=9Hz), 5.88 (1H, br.s), 3.80-2.50 (8H, m), 2.14 (3H, s)

35 Example 6

To a solution of N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide (769 mg) in N,N-dimethylformamide (8 ml) was added sodium hydride (116 mg, 60% oil dispersion) in one portion with stirring in an ice bath. The mixture was stirred for one hour at the same temperature and therein iodomethane (0.3 ml) was added.

40 After stirring for one hour in an ice bath, the mixture was concentrated in vacuo. The residue was purified by column chromatography on Dowex (50W x 8, H⁺) to give N-(4-acetyl-1-piperazinyl)-N-methyl-4-fluorobenzamide (440 mg).

mp : 205-206 °C

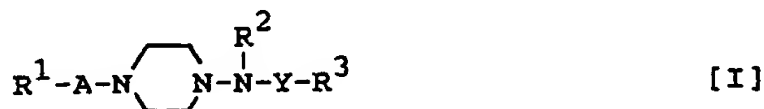
IR (CHCl₃) : 3010, 2960, 1652, 1612, 1570, 1508, 1440, 1344, 1268, 1154 cm⁻¹

45

Claims

1. A compound of the formula :

50



55

wherein R¹ is lower alkyl, aryl, ar(lower)alkoxy or a heterocyclic group, each of which may be substituted with halogen,
R² is hydrogen or lower alkyl,

R³ is cyclo(lower)alkyl, aryl or ar(lower)-alkyl, each of which may be substituted with halogen,
A is

5



10

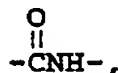
-SO₂- or lower alkylene, and
Y is



15

-SO₂- or

20



and pharmaceutically acceptable salts thereof.

25 2. A process for preparing a compound of the formula :

30



35

wherein R¹ is lower alkyl, aryl, ar(lower)alkoxy or a heterocyclic group, each of which may be substituted with halogen,
R² is hydrogen or lower alkyl,
R³ is cyclo(lower)alkyl, aryl or ar(lower)-alkyl, each of which may be substituted with halogen,
A is

40



45

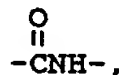
-SO₂- or lower alkylene, and
Y is



50

-SO₂- or

55



and pharmaceutically acceptable salts thereof, which comprises,

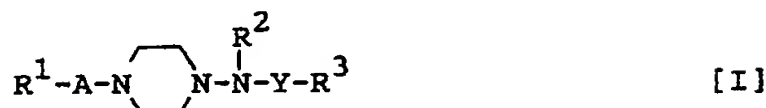
a) reacting a compound of the formula :



or its salt with a compound of the formula :



or its reactive derivative to provide a compound of the formula :



or its pharmaceutically acceptable salt,

in the above formulas, R^1 , R^2 , R^3 , A and Y are each as defined above,

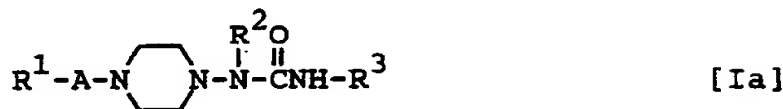
b) reacting a compound of the formula :



or its salt with a compound of the formula :



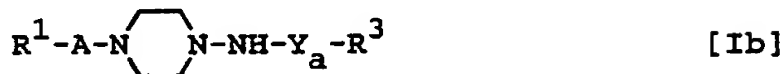
to provide a compound of the formula :



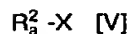
or its pharmaceutically acceptable salt,

in the above formulas, R^1 , R^2 , R^3 and A are each as defined above, or

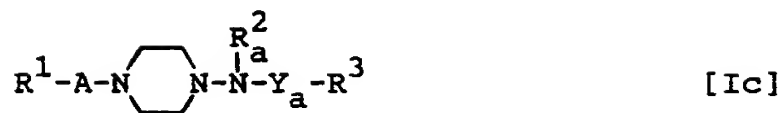
c) reacting a compound of the formula :



or its salt with a compound of the formula :



to provide a compound of the formula :



in the above formulas, R^1 , R^3 and A are each as defined above, R_a^2 is lower alkyl, Y_a is



or $-SO_2-$, and X is an acid residue.

3. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially nontoxic carrier or excipient.
4. A compound of claim 1 for use as a medicament.
5. A pharmaceutical composition according to claim 3 as a potentiating agent of the cholinergic activity.
6. A pharmaceutical composition according to claim 5 as a anti-amnesia agent or anti-dementia agent.
7. A method for therapeutic treatment of amnesia or dementia which comprises administering a compound of claim 1 to human beings.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP90/00898

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁴		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int. Cl ⁵ C07D295/32, A61K31/495		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC	C07D295/22-295/32, A61K31/495	
Documentation Searched other than Minimum Documentation to the extent that such documents are included in the fields searched ⁴		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁶		
Category ⁸	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	JP, B1, 39-19175 (GD Searle & CO.), 7 September 1964 (07. 09. 64) & US, A, 3,200,120 & US, A, 3,200,121 & GB, A, 996253	1, 2
A	JP, A1, 61-106570 (Bristol-Myers Co.), 24 May 1986 (24. 05. 86) & GB, A, 2,162,843	1 - 7
A	CA 108(5):37783g (Acta Pol. pharm., 43(5), 513-15(1986), Bulacinski et al.)	1 - 7
<p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"d" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
October 1, 1990 (01. 10. 90)	October 15, 1990 (15. 10. 90)	
International Searching Authority	Signature of Authorized Officer	
Japanese Patent Office		

Form PCT/ISA/210 (second sheet) (January 1983)



European Patent
Office

**SUPPLEMENTARY
EUROPEAN SEARCH REPORT**

436 734

Application Number

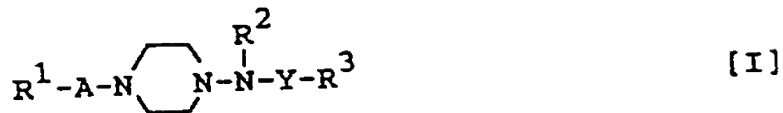
EP 90 91 0946

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	GB-A- 722 627 (CYANAMID) * Examples 20-22; claims * -----	1-4	C 07 D 295/32 A 61 K 31/495
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 D 295/00
The supplementary search report has been drawn up for the claims attached hereto.			
Place of search THE HAGUE		Date of completion of the search 16-10-1991	Examiner HELPS I.M.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

EPO FORM 150 (03.92) (P0004)

What we claim is :

1. A compound of the formula :



wherein R^1 is lower alkyl, aryl, ar(lower)alkoxy or a heterocyclic group, each of which may be substituted with halogen,

R^2 is hydrogen or lower alkyl,

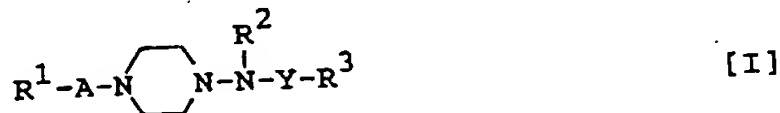
R^3 is cyclo(lower)alkyl, aryl or ar(lower)-alkyl, each of which may be substituted with halogen,

A is $\text{-}\overset{\text{O}}{\parallel}\text{C-}$, $\text{-SO}_2\text{-}$ or lower alkylene, and

Y is $\text{-}\overset{\text{O}}{\parallel}\text{C-}$, $\text{-SO}_2\text{-}$ or $\text{-}\overset{\text{O}}{\parallel}\text{CNH-}$,

and pharmaceutically acceptable salts thereof.

2. A process for preparing a compound of the formula :



wherein R^1 is lower alkyl, aryl, ar(lower)alkoxy or a heterocyclic group, each of which may be substituted with halogen,

R^2 is hydrogen or lower alkyl,

R^3 is cyclo(lower)alkyl, aryl or ar(lower)-alkyl, each of which may be substituted with halogen,

A is $\text{-}\overset{\text{O}}{\parallel}\text{C-}$, $\text{-SO}_2\text{-}$ or lower alkylene, and

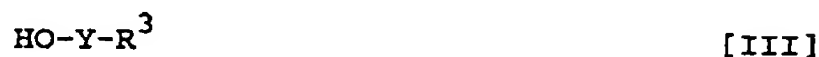
Y is $\overset{\text{O}}{\parallel}\text{-C-}$, $\text{-SO}_2\text{-}$ or $\overset{\text{O}}{\parallel}\text{-CNH-}$,

and pharmaceutically acceptable salts thereof, which comprises,

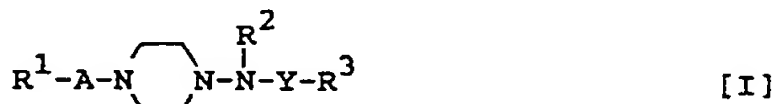
a) reacting a compound of the formula :



or its salt with a compound of the formula :



or its reactive derivative to provide a compound of the formula :



or its pharmaceutically acceptable salt, in the above formulas, R^1 , R^2 , R^3 , A and Y are each as defined above,

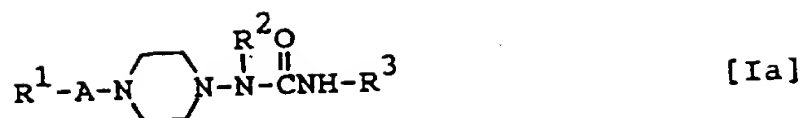
b) reacting a compound of the formula :



or its salt with a compound of the formula :

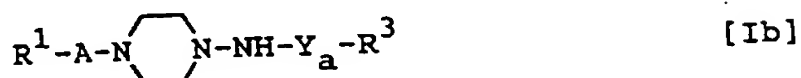


to provide a compound of the formula :



or its pharmaceutically acceptable salt,
in the above formulas, R^1 , R^2 , R^3 and A are each
as defined above, or

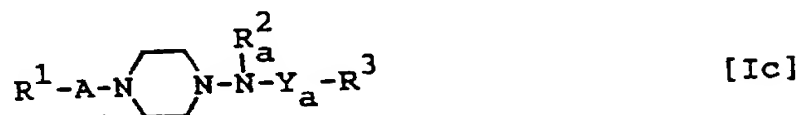
c) reacting a compound of the formula :



or its salt with a compound of the formula :



to provide a compound of the formula :



in the above formulas, R^1 , R^3 and A are each as
defined above, R_a^2 is lower alkyl, Y_a is

$\overset{\overset{O}{\parallel}}{C}-$ or $-SO_2-$, and X is an acid residue.

3. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially nontoxic carrier or excipient.
4. A compound of claim 1 for use as a medicament.
5. A pharmaceutical composition according to claim 3 as a potentiating agent of the cholinergic activity.

- 4 -
6. A pharmaceutical composition according to claim 5 as a anti-amnesia agent or anti-dementia agent.
 7. A method for therapeutic treatment of amnesia or dementia which comprises administering a compound of claim 1 to human beings.



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⑪ Publication number:

0 436 734 B1

⑫

EUROPEAN PATENT SPECIFICATION

④⑤ Date of publication of patent specification: **11.10.95** ⑤① Int. Cl.⁶: **C07D 295/32, A61K 31/495**

②① Application number: **90910946.4**

②② Date of filing: **12.07.90**

⑥⑥ International application number:
PCT/JP90/00898

⑥⑦ International publication number:
WO 91/01979 (21.02.91 91/05)

⑤④ NEW AMINOPIPERAZINE DERIVATIVES.

③③ Priority: **02.08.89 GB 8917687**

④③ Date of publication of application:
17.07.91 Bulletin 91/29

④⑤ Publication of the grant of the patent:
11.10.95 Bulletin 95/41

⑥④ Designated Contracting States:
CH DE DK FR GB IT LI SE

⑤⑤ References cited:
GB-A- 722 627
JP-A-61 106 570
JP-B- 3 919 175

**CA 108 (5): 37783g (Acta Pol. pharm., 43(5),
513-15 (1986), Bulacinski et al.)**

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EP 0 436 734 B1

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Description

TECHNICAL FIELD

5 This invention relates to new aminopiperazine derivatives and pharmaceutically acceptable salts thereof which are useful as a medicament.

BACKGROUND ART

10 Some piperazine derivatives have been known as useful anti-amnesia agents, for example, in G.B. Patent Application Publication No. 2 162 843 and EP Patent Application Publication No. 299 493, but the N-substituents of piperazine ring in these compounds do not contain amino group while our compounds are N-aminopiperazine derivatives.

15 Furthermore, GB-A-722,627 discloses 4-substituted-1-aminopiperazine derivatives, the substituent on 4-position of which is alkyl, aralkyl, monocyclic aryl, carbalkoxy, dialkylcarbamoyl or heterocyclic radical, and GB-A-996,253 also discloses 4-substituted-1-aminopiperazine derivatives, the substituent on 4-position of which is alkyl, hydroxyalkyl, benzyl, ar-methylbenzyl, ar-methoxybenzyl, ar-halobenzyl, benzhydryl or ar-chlorobenzhydryl. Moreover, it is not disclosed that 4-substituted-1-aminopiperazine derivatives in GB-A-722,627 and GB-A-996,253 are useful as an anti-amnesia agent or anti-dementia agent.

20

DISCLOSURE OF INVENTION

This invention relates to new aminopiperazine derivatives and pharmaceutically acceptable salts thereof.

25 More particularly, it relates to new aminopiperazine derivatives and pharmaceutically acceptable salts thereof which have the potentiation of the cholinergic activity, to processes for the preparation thereof, to a pharmaceutical composition comprising the same, and to a method for the treatment of disorders in the central nervous system for human beings, and more particularly to method for the treatment of amnesia, dementia and senile dementia.

30 One object of this invention is to provide new and useful aminopiperazine derivatives and pharmaceutically acceptable salts thereof which possess the potentiation of the cholinergic activity.

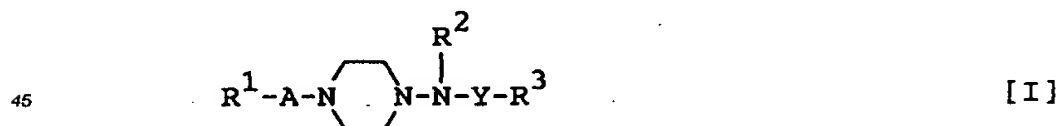
Another object of this invention is to provide processes for preparation of said aminopiperazine derivatives and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said aminopiperazine derivatives and pharmaceutically acceptable salts thereof.

35 Still further object of this invention is to provide a therapeutic method for the treatment of disorders in the central nervous system, for human beings, and more particularly of amnesia, dementia and senile dementia, using said aminopiperazine derivatives and pharmaceutically acceptable salts thereof.

The aminopiperazine derivatives of this invention are new and can be represented by the following general formula [I] :

40



wherein

50 R^1 is $\text{C}_1\text{-C}_6$ alkyl, aryl, $\text{ar}(\text{C}_1\text{-C}_6)$ alkoxy or a heterocyclic group, each of which may be substituted with halogen,

R^2 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl,

R^3 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or aryl, each of which may be substituted with halogen,

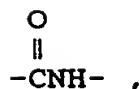
55 A is



Y or -SO₂-, and
is



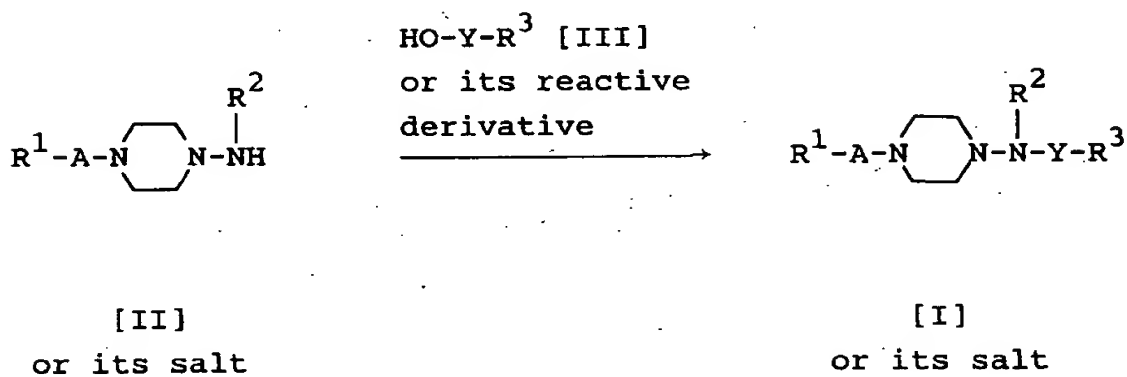
-SO₂- or

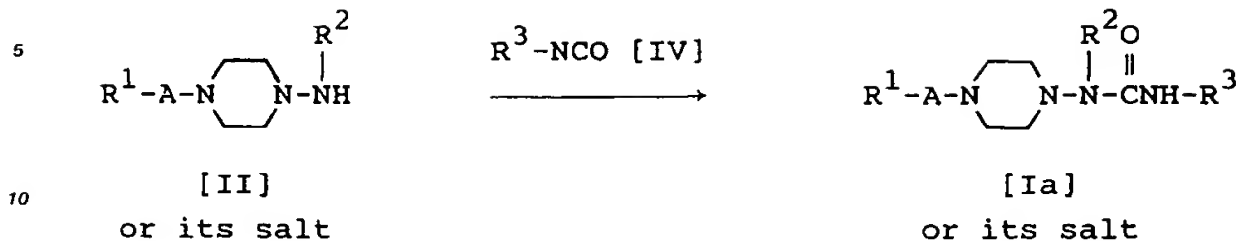
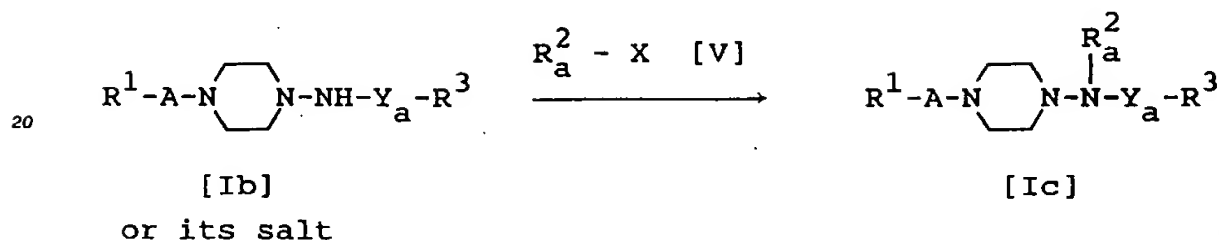


and pharmaceutically acceptable salts thereof.

The object compound [I] or its salt can be prepared by processes as illustrated in the following reaction schemes.

Process 1



Process 2Process 3

wherein

R¹, R², R³, A and Y are each as defined above,
 R_a² is C₁-C₆ alkyl,
 Y_a is



X or -SO₂-, and
 is an acid residue.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "C₁-C₆" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable "C₁-C₆ alkyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl, in which preferable one is methyl.

Suitable "aryl" may be phenyl, naphthyl, tolyl, xylyl, mesityl and cumenyl, in which preferable one is phenyl or naphthyl.

Suitable "ar(C₁-C₆)alkoxy" may be benzyloxy, phenethyloxy, phenylpropoxy, benzhydryloxy and trityloxy.

Suitable "heterocyclic group" may include saturated or unsaturated, monocyclic or polycyclic one containing at least one hetero atom such as nitrogen atom, oxygen atom or sulfur atom.

The preferred examples of thus defined "heterocyclic group" may be unsaturated, 3 to 8-membered, more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4-nitrogen atom(s), for example, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridyl N-oxide, dihydropyridyl, tetrahydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, tetrazinyl and tetrazolyl;

unsaturated, condensed heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl and benzotriazolyl;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl and oxadiazolyl;

saturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholino and sydnonyl;

unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl and benzoxadiazolyl;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl and thiadiazolyl;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl;

unsaturated, condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl and benzothiadiazolyl;

unsaturated, 3 to 8-membered heteromonocyclic group containing an oxygen atom, for example, furyl;

unsaturated, condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl;

unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s), for example, benzofuranyl.

Suitable "acid residue" may include halogen (e.g. fluorine, chlorine, bromine and iodine), arenesulfonyloxy (e.g., benzenesulfonyloxy and tosyloxy), C₁-C₆ alkanesulfonyloxy (e.g. mesyloxy and ethanesulfonyloxy).

The above-mentioned "C₁-C₆ alkyl", "aryl", "ar(C₁-C₆) alkoxy", "heterocyclic group", "cyclopropyl", "cyclobutyl", "cyclopentyl" and "cyclohexyl" may be substituted with halogen [e.g. fluorine, chlorine, bromine and iodine].

Suitable pharmaceutically acceptable salts of the object compound [I] are conventional non-toxic salts and include acid addition salt such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate and phosphate], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate and toluenesulfonate], a salt with an amino acid [e.g. aspartic acid salt and glutamic acid salt].

The processes for preparing the object compound [I] are explained in detail in the following.

Process 1

The compound [I] or its salt can be prepared by reacting a compound [II] or its salt with a compound [III] or its reactive derivative at the carboxy or sulfo group.

Suitable salts of the compound [II] may be the same as those exemplified for the compound [I].

Suitable reactive derivative at the carboxy or sulfo group of the compound [III] may include an ester, an acid halide and an acid anhydride. The suitable examples of the reactive derivatives may be an acid halide [e.g. acid chloride and acid bromide]; a symmetrical acid anhydride; a mixed acid anhydride with an acid such as aliphatic carboxylic acid [e.g. acetic acid and pivalic acid], substituted phosphoric acid [e.g. dialkylphosphoric acid and diphenylphosphoric acid];

an ester such as substituted or unsubstituted C₁-C₆ alkylester [e.g. methyl ester, ethyl ester, propyl ester, hexyl ester and trichloromethyl ester], substituted or unsubstituted ar(C₁-C₆)alkyl ester [e.g. benzyl ester, benzhydryl ester and p-chlorobenzyl ester], substituted or unsubstituted aryl ester [e.g. phenyl ester, tolyl ester, 4-nitrophenyl ester, 2,4-dinitrophenyl ester, pentachlorophenyl ester and naphthyl ester], or an ester with N,N-dimethylhydroxylamine, N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxy-6-chloro-1H-benzotriazole. These reactive derivatives can be optionally selected according to the kind of the compound [III] to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvents may be used in a mixture with water.

When the compound [III] is used in a free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, thionyl chloride, oxalyl chloride, C₁-C₆ alkoxycarbonyl halide [e.g. ethyl chloroformate and isobutyl chloroformate] and 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Process 2

The compound [Ia] or its salt can be prepared by reacting a compound [II] or its salt with a compound [IV].

5 Suitable salts of the compound [II] may be the same as those exemplified for the compound [I].

This reaction is usually carried out in a solvent such as dioxane, tetrahydrofuran, benzene, chloroform, methylene chloride or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

10

Process 3

The compound [Ic] can be prepared by reacting a compound [Ib] or its salt with a compound [V].

Suitable salts of the compound [Ib] may be the same as those exemplified for the compound [I].

15 The present reaction is preferably carried out in the presence of base such as an alkali metal (e.g. lithium, sodium and potassium), alkaline earth metal (e.g. calcium), alkali metal hydride (e.g. sodium hydride) and alkaline earth metal hydride (e.g. calcium hydride).

This reaction is usually carried out in a solvent such as N,N-dimethylformamide, diethyl ether, tetrahydrofuran, dioxane, benzene, toluene or any other solvent which does not adversely influence the reaction.

20 The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography and reprecipitation.

25 The object compounds [I] and pharmaceutically acceptable salts thereof possess strong potentiation of the cholinergic activity, and are useful for the treatment of disorders in the central nervous system for human beings, and more particularly of amnesia, dementia and senile dementia.

In order to illustrate the usefulness of the object compound [I], the pharmacological test data of the compound [I] are shown in the following.

30 Anti-scopolamine-induced amnesia activity

Test Method :

Male Wistar rats (body weight 250-300 g, 23-31 per group) were used. The effect of the test compound on deficit of memory induced by scopolamine (a muscarinic acetylcholine receptor antagonist) in passive avoidance task was examined. The apparatus consists of an illuminated compartment attached to a dark compartment equipped with a grid floor. These compartments are separated with a guillotine door. The rat was placed in the illuminated compartment and 10 seconds after placing the rat, the guillotine door was raised. After the rat entered into the dark compartment, the rat was returned to its home cage (Habituation). 30 minutes after habituation, scopolamine hydrobromide (1 mg/kg) (Sigma Co. St Louis, MO, U.S.A.) was intraperitoneally (i.p.) administered. 60 minutes after habituation, the acquisition trial was carried out. The rat was again placed in the illuminated chamber. When the rat entered in the dark chamber, the guillotine door was closed and a 4mA scrambled electrical footshock was delivered for 3 seconds through the grid floor. Test compounds were intraperitoneally administered immediately after this training.

45 In the test trial given 24 hours after the training, the rat was placed again in the illuminated compartment and the response latency to enter into the dark compartment was measured to an extent of 300 seconds at the longest. Results were recorded as the mean latency of step through for each experimental group of rats. The effect of the test compound was presented as a percentage of the recovery. The calculation was based on the following equation.

50

$$\text{Percentage of Recovery (\%)} = \frac{A - B}{300 - B} \times 100$$

55

A : mean latency of test compound (sec)
B : mean latency of vehicle (sec)

Test Compounds :

- (a) N-(4-Acetyl-1-piperazinyl)-4-fluorobenzamide
 (b) N-(4-Benzoyl-1-piperazinyl)-4-fluorobenzamide
 (c) N-(4-Acetyl-1-piperazinyl)-4-fluorobenzenesulfonamide

Test Results :

Percentage of Recovery (%)

Test Compound Dose (mg/kg)	(a)	(b)	(c)
0	0	0	0
0.1	23.0	26.4	20.4
0.32	24.6	29.5	26.8
1.0	40.3	19.7	34.5
3.2	39.2	41.5	50.2

For therapeutic purpose, the compound [I] and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solution, suspension or emulsion. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound [I], will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound [I] may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

To a mixture of 1-nitrosopiperazine (1.21 g) and pyridine (2.4 ml) in dioxane (18 ml) was added dropwise 2-thenoyl chloride (1.2 ml) in an ice bath. The mixture was stirred for one hour in an ice bath and then overnight at ambient temperature. The mixture was poured into a mixture of ethyl acetate (100 ml) and water (100 ml). The separated aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried and concentrated in vacuo. The residue was pulverized with diisopropyl ether to yield 1-nitroso-4-(2-thenoyl)-piperazine (1.78 g).

To a solution of 1-nitroso-4-(2-thenoyl)piperazine (1.78 g) in a mixture of acetic acid (8 ml) and water (8 ml) was added Zn powder (1.55 g) in several portions at 6-15°C. The suspension was stirred for 1.5 hours below 10°C. To the mixture was added acetic acid (4 ml) and Zn powder (780 mg) at 8-12°C. The mixture was stirred for 2 hours at ambient temperature. To the suspension was added 17% aqueous sodium hydroxide solution (70 ml). The insoluble materials were filtered off. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution by 5% methanol in dichloromethane) to yield 1-amino-4-(2-thenoyl)piperazine (1.17 g) as a pale yellow syrup.

¹H NMR (CDCl₃, δ) : 7.48 (1H, dd, J = 1 and 5Hz), 7.31 (1H, dd, J = 1 and 4Hz), 7.07 (1H, dd, J = 4 and 5Hz), 3.83 (4H, t, J = 5Hz), 2.88 (2H, br.s), 2.70 (4H, t, J = 5Hz)

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The following compound (Preparation 2) was obtained according to a similar manner to that of Preparation 1.

Preparation 2

1-Amino-4-(2-naphthoyl)piperazine

pale yellow syrup

^1H NMR (CDCl_3 , δ) : 7.98-7.83 (4H, m), 7.65-7.45 (3H, m), 3.88 (2H, br.s), 3.62 (2H, br.s), 3.04 (2H, br.s), 2.68 (4H, br.s)

Example 1

To a mixture of 1-acetyl-4-aminopiperazine dihydrochloride (540 mg) and 4-fluorobenzenesulfonyl chloride (535 mg) in dichloromethane (5 ml) was added triethylamine (1.2 ml) in a few minutes with stirring in an ice bath. After stirring for half an hour at the same temperature, the mixture was washed with brine, dried, and concentrated in vacuo. The residue was crystallized from ethanol and recrystallized from a mixture of ethanol and diethyl ether to yield N-(4-acetyl-1-piperazinyl)-4-fluorobenzenesulfonamide (360 mg) as white crystals.

mp : 185-186 °C

IR (CHCl_3) : 3400, 3300, 3005, 1642, 1638, 1596, 1498, 1460, 1256, 1240, 1170, 1155, 1094 cm^{-1}

Example 2

To a solution of 1-amino-4-benzoylpiperazine (1.1 g) and triethylamine (0.6 g) in dichloromethane (20 ml) was added dropwise 4-fluorobenzoyl chloride (0.86 g) with stirring in an ice bath. After stirring for one hour at the same temperature, the mixture was washed with 1N hydrochloric acid, dried, and concentrated in vacuo. The residue was crystallized from diisopropyl ether and purified by recrystallization from ethanol to give N-(4-benzoyl-1-piperazinyl)-4-fluorobenzamide (0.97 g) as white crystals.

mp : 206-207 °C

^1H NMR (CDCl_3 , δ) : 7.78 (2H, dd, J = 5 and 9Hz), 7.43 (5H, s), 7.34 (1H, br.s), 7.12 (2H, t, J = 9Hz), 3.96 (2H, br.s), 3.67 (2H, br.s), 3.03 (4H, br.s)

The following compound (Example 3) was obtained according to a similar manner to that of Example 1.

Example 3

N-(4-Benzenesulfonyl-1-piperazinyl)-4-fluorobenzenesulfonamide

mp : 190-191 °C

^1H NMR (CDCl_3 - CD_3OD = 1:1, δ) : 7.88 (2H, dd, J = 5 and 9Hz), 7.78-7.57 (5H, m), 7.20 (2H, t, J = 9Hz), 3.03-2.92 (4H, m), 2.75-2.66 (4H, m)

The following compounds (Examples 4-1) to 4-9)) were obtained according to a similar manner to that of Example 2.

Example 4

1) N-(4-Acetyl-1-piperazinyl)-2-fluorobenzamide

mp : 171-172 °C

IR (CHCl_3) : 3480, 3400, 3015, 1678, 1644, 1619, 1488, 1458, 1444, 1300, 1285, 1262 cm^{-1}

2) N-(4-Acetyl-1-piperazinyl)-3-fluorobenzamide

mp : 196-197 °C

IR (CHCl_3) : 3350, 3005, 1680, 1640, 1592, 1440, 1282, 1258 cm^{-1}

3) N-(4-Acetyl-1-piperazinyl)-4-fluorobenzamide

mp : 211-212 °C

^1H NMR ($\text{DMSO}-d_6$, δ) : 9.58 (1H, s), 7.84 (2H, dd, J = 6 and 9Hz), 7.31 (2H, t, J = 9Hz), 3.52 (4H, t, J = 6Hz), 2.88 (2H, t, J = 6Hz), 2.82 (2H, t, J = 6Hz), 2.03 (3H, s)

4) N-(4-Acetyl-1-piperazinyl)cyclohexanecarboxamide

mp : 220-221 °C

IR (CHCl_3) : 3430, 3340, 2998, 2940, 2852, 1638, 1448, 1280, 1256, 1140, 1118, 998 cm^{-1}

5) N-(4-Phenylsulfonyl-1-piperazinyl)-4-fluorobenzamide

mp : 274-276 °C

¹H NMR (CDCl₃-CD₃OD = 1:1, δ) : 7.86-7.58 (7H, m), 7.14 (2H, t, J=9Hz), 3.28-3.18 (4H, m), 3.07-2.98 (4H, m)

6) N-(4-Methylsulfonyl-1-piperazinyl)-4-fluorobenzamide

mp : 257-258 °C

¹H NMR (CDCl₃-CD₃OD = 1:1, δ) : 7.80 (2H, dd, J=5 and 9Hz), 7.12 (2H, t, J=9Hz), 3.40 (4H, t, J=5Hz), 2.99 (4H, t, J=5Hz), 2.88 (3H, s)

7) N-[4-(2-Thenoyl)-1-piperazinyl]-4-fluorobenzamide

mp : 189-190 °C

IR (CHCl₃) : 3440, 3340, 3280, 3000, 1674, 1604, 1501, 1438, 1284, 1259 cm⁻¹

8) N-[4-(2-Naphthoyl)-1-piperazinyl]-4-fluorobenzamide

mp : 227-228 °C

IR (CHCl₃) : 3430, 3335, 2990, 1668, 1617, 1601, 1496, 1477, 1438, 1284, 1260 cm⁻¹

9) N-(4-Benzyl-1-piperazinyl)-4-fluorobenzamide

mp : 165-168 °C

¹H NMR (CDCl₃, δ) : 7.77 (2H, dd, J=5 and 9Hz), 7.45-7.23 (5H, m), 7.10 (2H, t, J=9Hz), 3.41 (2H, s), 3.00 (4H, br.s), 2.72 (4H, br.s)Example 5

To a solution of 1-acetyl-4-aminopiperazine dihydrochloride (540 mg) in dichloromethane (5 ml) was added dropwise triethylamine (0.8 ml) followed by addition a solution of 4-fluorophenylisocyanate (377 mg) in dichloromethane (2.5 ml) with stirring in an ice bath. After stirring for 100 minutes at the same temperature, a mixture of dichloromethane (15 ml) and methanol (3 ml) was added to the reaction mixture. The mixture was washed with brine, dried, and concentrated in vacuo. The residue was crystallized from ethanol to yield N-(4-acetyl-1-piperazinyl)-N'-(4-fluorophenyl)urea (500 mg).

mp : 210-211 °C

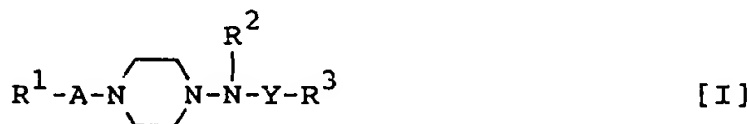
¹H NMR (CDCl₃, δ) : 7.98 (1H, s), 7.40 (2H, dd, J=5 and 9Hz), 7.00 (2H, t, J=9Hz), 5.88 (1H, br.s), 3.80-2.50 (8H, m) 2.14 (3H, s)Example 6

To a solution of N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide (769 mg) in N,N-dimethylformamide (8 ml) was added sodium hydride (116 mg, 60% oil dispersion) in one portion with stirring in an ice bath. The mixture was stirred for one hour at the same temperature and therein iodomethane (0.3 ml) was added. After stirring for one hour in an ice bath, the mixture was concentrated in vacuo. The residue was purified by column chromatography on Dowex (50W x 8, H⁺) to give N-(4-acetyl-1-piperazinyl)-N-methyl-4-fluorobenzamide (440 mg).

mp : 205-206 °C

IR (CHCl₃) : 3010, 2960, 1652, 1612, 1570, 1508, 1440, 1344, 1268, 1154 cm⁻¹Claims

1. A compound of the formula :



wherein

R¹ is C₁-C₆ alkyl, aryl, ar(C₁-C₆)alkoxy or a heterocyclic group, each of which may be substituted with halogen,R² is hydrogen or C₁-C₆ alkyl,R³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or aryl, each of which may be substituted

A with halogen,
is

5



10

Y

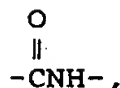
or -SO₂-, and
is

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-SO₂- or

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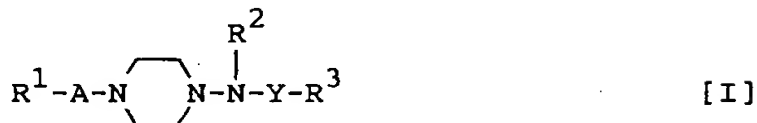


and pharmaceutically acceptable salts thereof.

25

2. A process for preparing a compound of the formula :

30



35

wherein

R¹ is C₁-C₆ alkyl, aryl, ar(C₁-C₆)alkoxy or a heterocyclic group, each of which may be substituted with halogen,

R² is hydrogen or C₁-C₆ alkyl,

40

R³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or aryl, each of which may be substituted with halogen,

A is

45



Y

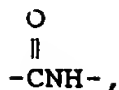
or -SO₂-, and
is

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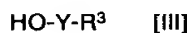
-SO₂- or



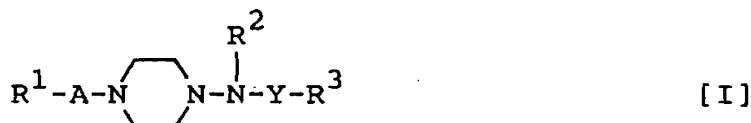
and pharmaceutically acceptable salts thereof, which comprises,
a) reacting a compound of the formula :



or its salt with a compound of the formula :



or its reactive derivative to provide a compound of the formula :



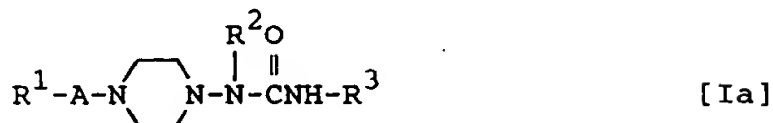
or its pharmaceutically acceptable salt,
in the above formulas, R^1 , R^2 , R^3 , A and Y are each as defined above,
b) reacting a compound of the formula :



or its salt with a compound of the formula :

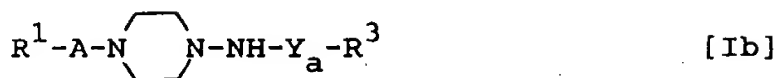


to provide a compound of the formula :



or its pharmaceutically acceptable salt,
in the above formulas, R^1 , R^2 , R^3 and A are each as defined above, or

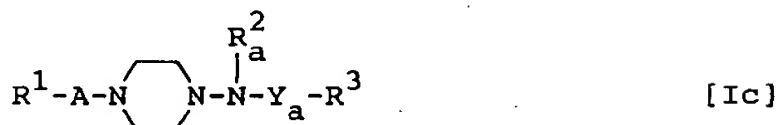
c) reacting a compound of the formula :



or its salt with a compound of the formula :



to provide a compound of the formula :



in the above formulas, R^1 , R^3 and A are each as defined above, R_a^2 is C_1-C_6 alkyl, Y_a is



or $-SO_2-$, and X is an acid residue.

3. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially nontoxic carrier or excipient.
4. A compound of claim 1 for use as a medicament.
5. A pharmaceutical composition according to claim 3 as a potentiating agent of the cholinergic activity.
6. A pharmaceutical composition according to claim 5 as an anti-amnesia agent or anti-dementia agent.
7. A compound according to claim 1, wherein
 - R^1 is C_1-C_6 alkyl, phenyl, naphthyl or thienyl, and
 - R^3 is phenyl which may be substituted with halogen.
8. A compound according to claim 7, wherein
 - R^2 is hydrogen,
 - R^3 is phenyl which is substituted with halogen, and
 - Y is



or $-SO_2-$.

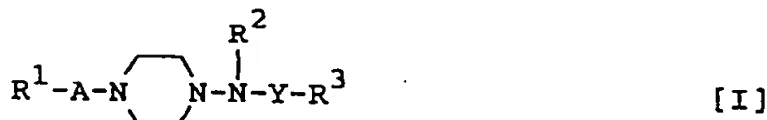
9. A compound of claim 8, which is N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide.

10. A compound of claim 8, which is N-(4-benzoyl-1-piperaziny)-4-fluorobenzamide.

11. A compound of claim 8, which is N-(4-acetyl-1-piperaziny)-4-fluorobenzenesulfonamide.

5 Patentansprüche

1. Verbindung der Formel



worin bedeuten:

- R¹ C₁-C₆-Alkyl, Aryl, Ar(C₁-C₆)-alkoxy oder eine heterocyclische Gruppe, von denen jeder Rest durch Halogen substituiert sein kann,
- R² Wasserstoff oder C₁-C₆-Alkyl,
- R³ Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder Aryl, von denen jeder Rest durch Halogen substituiert sein kann,
- A



oder -SO₂- und

Y

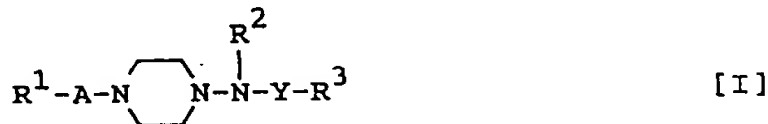


-SO₂- oder



und ihre pharmazeutisch akzeptablen Salze.

2. Verfahren zur Herstellung einer Verbindung der Formel



worin bedeuten:

- R¹ C₁-C₆-Alkyl, Aryl, Ar(C₁-C₆)-alkoxy oder eine heterocyclische Gruppe, von denen jeder Rest durch Halogen substituiert sein kann,

R² Wasserstoff oder C₁-C₆-Alkyl,
 R³ Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder Aryl, von denen jeder Rest durch Halogen substituiert sein kann,

A

5



10

oder -SO₂- und

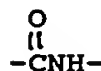
Y

15



-SO₂- oder

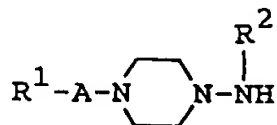
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25

und ihrer pharmazeutisch akzeptablen Salze, das umfaßt
 a) die Umsetzung einer Verbindung der Formel

30



[II]

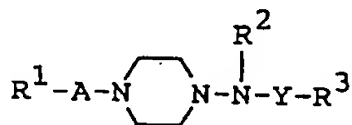
35

oder ihres Salzes mit einer Verbindung der Formel

HO-Y-R³ [III]

oder ihres reaktionsfähigen Derivats unter Bildung einer Verbindung der Formel

40

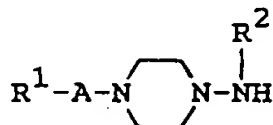


[I]

45

oder ihres pharmazeutisch akzeptablen Salzes,
 wobei in den obengenannten Formeln R¹, R², R³, A und Y jeweils wie oben definiert sind,
 b) die Umsetzung einer Verbindung der Formel

50



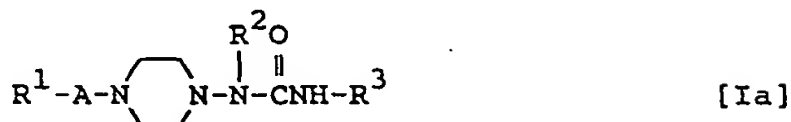
[II]

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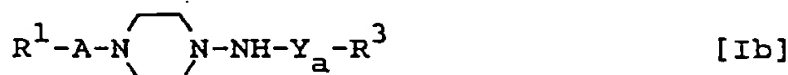
oder ihres Salzes mit einer Verbindung der Formel



unter Bildung einer Verbindung der Formel



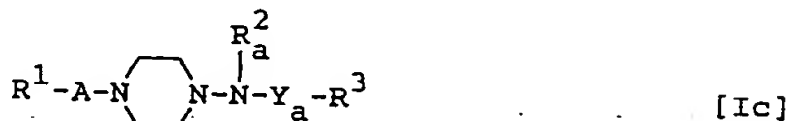
oder ihres pharmazeutisch akzeptablen Salzes,
wobei in den obengenannten Formeln R^1 , R^2 , R^3 und A jeweils wie oben definiert sind, oder
c) die Umsetzung einer Verbindung der Formel



oder ihres Salzes mit einer Verbindung der Formel



unter Bildung einer Verbindung der Formel



wobei in den obengenannten Formeln R^1 , R^3 und A jeweils wie oben definiert sind, R_a^2 für C_1 - C_6 -Alkyl, Y_a für



oder $-SO_2$ - und X für einen Säurerest stehen.

3. Pharmazeutische Zusammensetzung, die eine Verbindung nach Anspruch 1 als einen aktiven Bestandteil (Wirkstoff) in Assoziation (Kombination) mit einem pharmazeutisch akzeptablen, im wesentlichen nicht-toxischen Träger oder Exzipienten enthält.
4. Verbindung nach Anspruch 1 für die Verwendung als Arzneimittel.
5. Pharmazeutische Zusammensetzung nach Anspruch 3 als Mittel zur Potenzierung (Verstärkung) der cholinergischen Aktivität.
6. Pharmazeutische Zusammensetzung nach Anspruch 5 als Antiarnesie-Mittel oder Antidemenz-Mittel.
7. Verbindung nach Anspruch 1, worin bedeuten:
 R^1 C_1 - C_6 -Alkyl, Phenyl, Naphthyl oder Thienyl und

R³ Phenyl, das durch Halogen substituiert sein kann.

8. Verbindung nach Anspruch 7, worin bedeuten:

R² Wasserstoff,

R³ Phenyl, das durch Halogen substituiert ist, und

Y



oder -SO₂-.

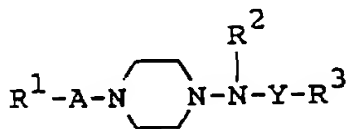
9. Verbindung nach Anspruch 8, bei der es sich handelt um N-(4-Acetyl-1-piperazinyl)-4-fluorobenzamid.

10. Verbindung nach Anspruch 8, bei der es sich handelt um N-(4-Benzoyl-1-piperazinyl)-4-fluorobenzamid.

11. Verbindung nach Anspruch 8, bei der es sich handelt um N-(4-Acetyl-1-piperazinyl)-4-fluorobenzolsulfonamid.

Revendications

1. Composé répondant à la formule :



[I]

dans laquelle R¹ est un groupe alkyle en C₁-C₆, aryle, ar(alcoxy en C₁-C₆) ou un groupe hétérocyclique, dont chacun peut être substitué par un atome d'halogène, R² est un atome d'hydrogène ou un groupe alkyle en C₁-C₆, R³ est un groupe cyclopropyle, cyclobutyle, cyclopentyle, cyclohexyle ou aryle, dont chacun peut être substitué par un atome d'halogène,

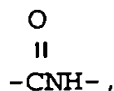
A est



ou -SO₂- et
Y est

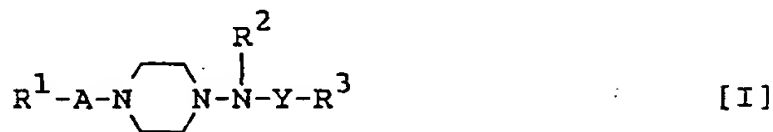


-SO₂- ou



et des sels pharmaceutiquement acceptables de celui-ci.

2. Procédé pour préparer un composé répondant à la formule :



dans laquelle R¹ est un groupe alkyle en C₁-C₆, aryle, ar(alcoxy en C₁-C₆) ou un groupe hétérocyclique, dont chacun peut être substitué par un atome d'halogène,

R² est un atome d'hydrogène ou un groupe alkyle en C₁-C₆,

R³ est un groupe cyclopropyle, cyclobutyle, cyclopentyle, cyclohexyle ou aryle, dont chacun peut être substitué par un atome d'halogène,

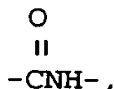
A est



ou -SO₂- et
Y est



-SO₂- ou



et des sels pharmaceutiquement acceptables de celui-ci, qui consiste à :

a) faire réagir un composé répondant à la formule :

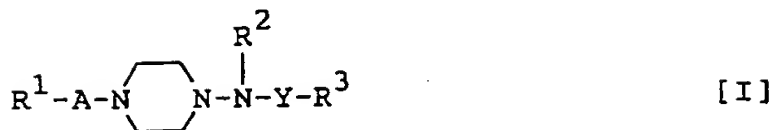


ou son sel avec un composé répondant à la formule :



ou son dérivé réactif pour fournir un composé répondant à la formule :

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ou son sel pharmaceutiquement acceptable,
dans les formules ci-dessus, R^1 , R^2 , R^3 , A et Y sont chacun tels que définis ci-dessus,
b) faire réagir un composé répondant à la formule :

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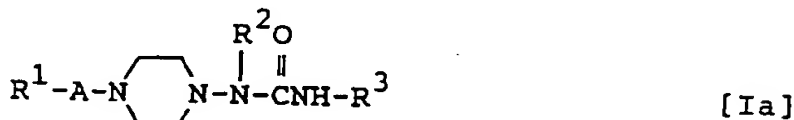
ou son sel avec un composé répondant à la formule :



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pour fournir un composé répondant à la formule :

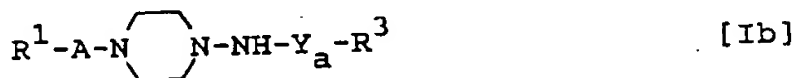
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ou son sel pharmaceutiquement acceptable,
dans les formules ci-dessus, R^1 , R^2 , R^3 et A sont chacun tels que définis ci-dessus, ou
c) faire réagir un composé répondant à la formule :

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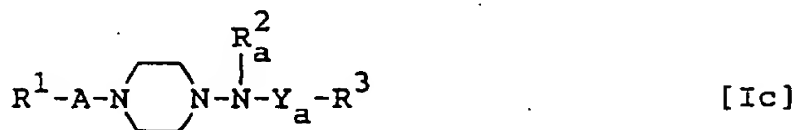
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ou son sel avec un composé répondant à la formule :



pour fournir un composé répondant à la formule :

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dans les formules ci-dessus, R^1 , R^3 et A sont chacun tels que définis ci-dessus, R_a^2 est un groupe alkyle en C_1-C_6 , Y_a est :



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ou -SO₂-, et X est un résidu acide.

3. Composition pharmaceutique comprenant un composé de la revendication 1, comme ingrédient actif,
10 en association avec un support ou excipient pharmaceutiquement acceptable, sensiblement non toxique.
4. Composé selon la revendication 1 pour emploi comme médicament.
5. Composition pharmaceutique selon la revendication 3, comme agent renforçant l'activité cholinergique.
- 15 6. Composition pharmaceutique selon la revendication 5 comme agent anti-amnésie ou agent antidémence.
7. Composé selon la revendication 1, dans lequel R¹ est un groupe alkyle en C₁-C₆, phényle, naphthyle ou
20 thiényl, et R³ est un groupe phényle qui peut être substitué par un atome d'halogène.
8. Composé selon la revendication 7, dans lequel R² est un atome d'hydrogène, R³ est un groupe phényle qui est substitué par un atome d'halogène, et
Y est

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30

ou -SO₂-.

9. Composé selon la revendication 8 qui est le N-(4-acétyl-1-pipérazinyl)-4-fluorobenzamide.
- 35 10. Composé selon la revendication 8, qui est le N-(4-benzoyl-1-pipérazinyl)-4-fluorobenzamide.
11. Composé selon la revendication 8, qui est le N-(4-acétyl-1-pipérazinyl)-4-fluorobenzènesulfonamide.

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